THE ROLE OF MATHEMATICAL MODELING IN EVIDENCE-BASED MALARIA CONTROL

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Abstract. Mathematical models have long provided basic insights for malaria control. The recent success of the Onchocerciasis Control Program in west Africa shows that models can make great pragmatic contributions to intervention programs if the modeling is integrated into the overall program, and if the participants are clear about what models can and cannot do. This lesson can be applied to evidence-based malaria control.

HISTORY

"Among the many fads in the medical profession to-day...is the theory...that anopheles is the means of the distribution of the plasmodium of malaria. I shall show by statistics that malaria is a water-borne complaint…" (Hurley, 1905)[1]

Clearly, Dr. Hurley's statistics did not tell the whole story: what he called a medical "fad" is a fact. Ronald Ross, who had demonstrated eight years previously that malaria is transmitted by *Anopheles* mosquitoes, also developed the first mathematical model of malaria transmission and emphasized that "the mathematical method of treatment is really nothing but the application of careful reasoning to the problems at issue."[2]

That kind of modeling, what Ross called "*a priori*" modeling, produces models that embody hypotheses about how the world works: that is, the models represent in mathematical form our ideas about the underlying mechanisms and interactions that generate the phenomena we are investigating. Those sorts of models are used every day. They are familiar, highly-valued tools in engineering and business, and in most sciences, but they remain rare in the biomedical research and public health communities.

Ross used his models to arrive at important practical conclusions such as that, "…to counteract malaria anywhere we need not banish *Anopheles* there entirely…we need only to reduce their numbers below a certain figure."[3] This idea about threshold densities of *Anopheles* was tested successfully.[4] Ross also used a model to conclude that control programs that integrated vector reduction (larvicides), drug treatment (quinine), and personal protection (bed nets) were much more likely to succeed than efforts that relied on just one intervention measure.[2] Only a few of his contemporaries paid attention to such ideas. Some incorporated them in successful programs of environmental management,[5–7] but Ross' models, and practical conclusions. were largely ignored.

In the 1950s, when George Macdonald returned to England from years of work in the tropics, and began to build on Ross' models, he had a similarly practical perspective, and similar aims. He too expected "theory," *a priori* models, to serve highly practical purposes in intervention programs: "When a method is chosen, theory acts as a guide to the degree of efficiency to be demanded of it and as a background to the examination of both success and failure."[8]

Macdonald's models indicated that at equilibrium, the weakest link in the chain of malaria transmission was the survivorship of adult female *Anopheles*. Given that his models were published at about the same time the global eradication campaign based on DDT began, with DDT targeted at adult female *Anopheles*, it is not surprising that this conclusion was recruited to the cause. What Macdonald actually wrote suggests more insight and caution, but it may be that he too got caught up in the appeal of DDT as a "silver bullet."

In any case, the Ross and Macdonald models were based on the sort of structure sketched in Figure 1: the assumption is that at any given moment an entire population can be divided into distinct compartments, of the susceptible, the infected and the infectious, and that infection spreads by random contact between the appropriate susceptible and infectious "compartments" of the human and mosquito populations.

RECENT DEVELOPMENTS

By the 1970s, it was clear that Macdonald's model could be greatly improved by adding explicit considerations of human immunity, at which point, as part of the Garki project in Nigeria, Dietz and Molineaux developed a more sophisticated model. That model, in their words, did a "fairly realistic" job of simulating malaria epidemiology at Garki, given entomologic inputs, and provided conditional, comparative forecasts for several specific interventions.[9] In the 1980s, Halloran and others took another step by explicitly considering the population-level effects of potential stage-specific vaccines.[10]

Malaria modeling has moved on from there, of course, most recently in line with an observation Macdonald made at the very end of his life: "…a powerful tool for the design of eradication and control programs, and for the analysis of difficulties in them, could be produced by the extension of dynamic studies using computer techniques."[11]

The power of modern computers has allowed the basic ideas of the compartment models to be taken down to the level of individuals, such that interacting populations are modeled as large numbers of interacting individual humans and individual mosquitoes, each with its own characteristics and dynamics, between whom parasite genotypes, each with its own characteristics and dynamics, can be transmitted. Further steps toward biologic realism have begun to include the effects of seasonality, meiotic recombination among parasites, immunologic cross-reactivity, and other factors.[12]

Now that malaria research and malaria control are beginning to gain attention again, however, we should focus more effort and more resources toward pragmatic, intervention-focused modeling: we must make sure that malaria research and malaria control benefit more directly from the best tools available.[13,14]

The best recent example of pragmatic, effective intervention-focused modeling comes not from malaria, but from the
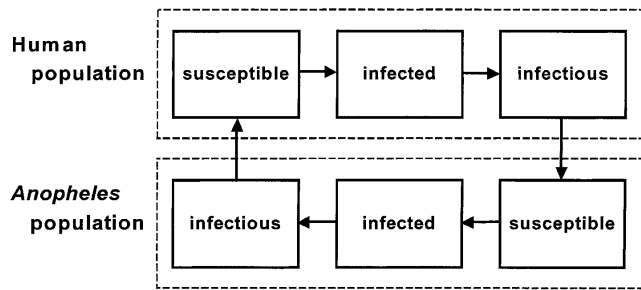
FIGURE 1. Schematic of the Ross-Macdonald models. Recent models have added explicit representations of human immunity, and have considered populations as aggregates of individuals rather than as compartments (see text).

Onchocerciasis Control Program (OCP) in west Africa. The OCP has been extremely successful, and there is no question that its success can be attributed partly to its modeling component.[15,16] What is important is not so much the details of those models, although they are good ones, or any specific results, although there were extremely important ones, but the fact that modeling was closely integrated with every part of research and operations. As the modelers pointed out, "modeling should be an integral part of the disease control program. This calls for a system that is easy to use and that can be adapted to new results and to changes in control policy."[17] The OCP models were developed and tested as a team effort, not in abstraction; they were seen and used on an every-day basis, as working tools.

Their success came despite much initial skepticism within OCP. Furthermore, modeling started at a time when the future of the program itself was in very serious doubt: those directly involved felt that a good job was being done, but the principals could not be convinced. The models helped to convince donors and the scientific community that there was progress, and, very important, that there could be a successful end if certain conditions were satisfied, conditions that were clearly spelt out in the models. The modeling brought together all of the different scientists in OCP, i.e., epidemiologists, entomologists, economists, etc., as well as the operations managers, and, by bringing all of the relevant data together, modeling convincingly predicted eventual success. The impact of this on the morale of all concerned was incalculable. When OCP was finally terminated, in 2002, it was universally regarded as a successful public health program. Modeling has retained a prominent role in follow-up policy discussions.[18] It is time that we adopt this approach in malaria, and start using mathematical models as tools in the fight.

UNDERSTANDING AND USING MODELS

It is critically important for modelers to remember, and non-modelers to understand, what models can and cannot do in this sort of context. We need to have realistic expectations. In particular, in this context, models cannot provide accurate numerical predictions of outcomes: they can be used to forecast, but only in fairly gross terms. The biologic, social, and other systems involved are sufficiently complex that it may not be possible to even define all of the variables, much less get precise predictions about their interactions and overall results in a specific real-world situation. Thus, the key is to

look for large differences between different models, and between different interventions in the same modeling scenario. That is, mathematical models can be used to 1) systematically compare alternate strategies, 2) determine the key issues in decision-making, and 3) identify gaps in current knowledge.

Mathematical models can help us figure out which decisions will have the largest impacts on outcomes and can provide comprehensive examinations of the assumptions that enter into decisions in a way that purely verbal reasoning and debate cannot.

It is important to recognize that a great deal can be learned from examining the differences as well as the similarities between models. Figure 2 illustrates this point, with hypothetical output from hypothetical models. On the horizontal x-axis is the percentage of the population covered by some intervention, say bed nets, or a drug, or a vaccine. On the vertical y-axis is the resulting percentage reduction in mortality. At 0% coverage, we see that there is no change, 0%, in the number of deaths, and as we get close to 100% coverage, we get close to a 100% reduction, i.e., no deaths at all. Both models agree on that, which is what we would expect: the more people covered the fewer the deaths.

However, there are clear differences between the model results as well. For instance, what level of coverage might cut casualties by a half? According to model A, a little less than 30% does the job; according to model B, a little more than 70% is needed. But remember what these sorts of models do: they embody hypotheses about underlying mechanisms and interactions. Thus, these differences might have to do with two different ideas about how this intervention works in particular sub-populations, or at particular sites, or with two different ideas about whether this and some other intervention act synergistically.

Those different ideas are right there in the models explicitly: you know what the different assumptions are, why the modelers put them there, what data they are based on. Hopefully, if need be, you can find ways to test them. The results you want to rely on in decision making, of course, are those on which a number of different models agree, again, agree in general terms, if not in detailed predictions. However, when models disagree, assuming that they have been produced by
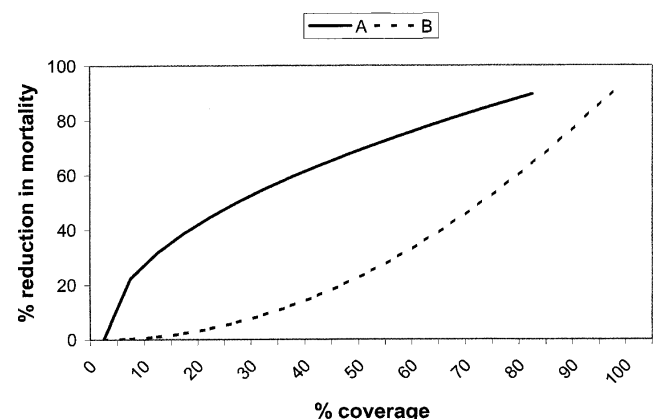

FIGURE 2. Hypothetical output from two hypothetical models. The horizontal x-axis shows the percentage of the population covered by an intervention and the vertical y-axis shows the resulting percentage reduction in mortality (see text).

competent, honest modelers, that typically tells you a great deal about the information that you will have to use to make your decisions in any case: What are the assumptions? What are the most critical gaps and uncertainties in the data? Why is there disagreement?

In non-malarious regions, enormous sums are invested in modeling economies, and weather, although the models are obviously wrong, and far too many real-world variables are involved to ever get the models really right. We do that because the stakes are so high, and we cannot wait for "perfect" models to magically appear, any more than we can in engineering, or business, or war. Weather modeling has greatly improved, in fact, precisely because models are used in conjunction with empirical research to gain greater understanding of the underlying mechanisms and interactions that produce weather. We must take advantage of similar approaches and similar tools in malaria control because we cannot afford not to.

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